REMARKS

This reply is being submitted with a Request for Continued Examination. Following entry of the amendment, claims 1-7, 10, 11, and 21-26 will be pending in this application. Claims 1, 10, and 11 are currently amended, and new claims 25 and 26 are added. Support for the amendments and new claims can be found throughout the specification and claims as originally filed, e.g., at paragraphs [0025], [0027], and [0047]. No new matter has been added.

Applicants acknowledge and thank the Examiner for withdrawal of the prior rejections for alleged anticipation, obviousness, and indefiniteness.

35 USC § 103

Claims 1-3, 10 and 11 were rejected as allegedly unpatentable over U.S. Patent Application Publication 2002/0119121 ("Vitiello"), in view of Friedman et al., 2000, Clin. Cancer Res., 6:2585-97 ("Friedman"). Applicants respectfully traverse.

In the interest of proceeding toward allowance, applicants have amended claim 1 to recite a cancer of the central nervous system rather than any disease condition, and to recite that the administration of chemotherapy occurs after the administration of a vaccination of dendritic cells (DC). Applicants submit that the claims as amended are patentable over the combination of Vitiello and Friedman

First, a legal point. The Office action (at page 4) points to *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) as support for the position that "it is prima facie obvious to combine two modes of treatment" (emphasis added). However, it should be noted that *Kerkhoven* did not relate to unpredictable methods of medical treatment. The claims at issue in *Kerkhoven* were directed to predictable processes for producing detergent mixtures. In fact, the dissent points out that "the uncertainty and unpredictability often associated with the chemical arts is not present here." 204 USPQ at 1075. Because one skilled in the art would not have been able to predict that administration of chemotherapy after a DC vaccination would have significantly improved survival or time to recurrence as compared to chemotherapy without vaccination, the reasoning of *Kerkhoven* is not relevant to the instant claims.

Second, the facts show that there is a long-felt but unsolved need for effective central nervous system (CNS) cancer therapies, and that applicants have provided evidence of unexpectedly beneficial results in the battle against these devastating forms of cancer. The instant specification teaches that "GBM [glioblastoma multiforme] diagnosis carries with it an average survival between twelve and eighteen months (with 90-95% [of] patients surviving less than two years), without the possibility of spontaneous remission or effective treatment" ([0004]). Stupp et al., 2003, "Recent Developments in the Management of Malignant Glioma," American Society of Clinical Oncology Educational Book (previously of record in the IDS mailed February 21, 2008), similarly teaches that "[d]espite advances in surgery and radiotherapy, [malignant glioma] tumors will invariably recur with an ultimately fatal outcome" (abstract). Stupp et al. further states that "[a] systematic and integrated approach in developing new treatment modalities and translational research is required for clinically relevant advances in this disease" (abstract). Thus, at the time of the present application, there was a need for life-extending therapies for CNS cancer, and in particular for GBM.

In view of the unpredictability inherent in therapy for cancer of the central nervous system and the long-felt need for improved therapeutics, applicants' experimental results described in the specification are truly surprising. As described in Examples 1 and 2 of the application, newly diagnosed GBM patients were administered surgical resection and standard radiation therapy, followed by either administration of chemotherapy or vaccination with DCs ([0044], Fig. 1A). Both the vaccine and chemotherapy groups had similar times of progression to an initial disease recurrence ([0046], Fig. 1B). Following an initial recurrence, patients in the vaccine+chemotherapy group were then administered a course of chemotherapy (see Fig. 1A). Strikingly, the average time to subsequent recurrence in patients administered chemotherapy following vaccination (about 13 months) was significantly increased compared to both initial recurrence in all groups (about 7-8 months) and the subsequent recurrences in the vaccine (about 6 months) and chemotherapy (about 3 months) groups (see Fig. 1B). Therefore, administration of chemotherapy following vaccination provided a significant delay in progression of the disease as compared to chemotherapy or vaccination alone.

Additionally, GBM patients receiving chemotherapy after vaccination enjoyed significantly prolonged survival relative to patients receiving either treatment individually

([0045], Figs. 2 and 5). The mean survival of the vaccine+chemotherapy group was significantly longer (26 ± 3.7 months) as compared to the mean survival of the either the vaccine only or chemotherapy only group (17.9 ± 1.7 and 15.9 ± 2.1 months, respectively). Some patients administered the sequential therapy survived for three or four years, whereas there were no three-year survivors in the vaccine or chemotherapy group ([0048]). In addition, tumor regression was observed in three of the thirteen patients receiving the vaccine and chemotherapy treatment, apparently the first demonstration of objective regression in an adoptive immunotherapy setting ([0047]). In view of the teaching of the specification that "GBM diagnosis carries with it an average survival between twelve and eighteen months (with 90-95% [of] patients surviving less than two years), without the possibility of spontaneous remission or effective treatment," these findings of increased survivorship and tumor regression are truly remarkable. Although a cure is still a ways off, the increase in life by an average of eight months compared to other therapies is a significant, and unexpected, improvement in therapy for GBM.

The Office action (at page 11) states that:

> Although the specification discloses significantly improved outcome for patients receiving DC vaccination followed by chemotherapy compared to patients treated with either alone, it appears the combination of chemotherapy and DC vaccination results in the improvement and no comparison is made to suggest that the sequence of administration of DC before chemotherapy gives unexpected results because no comparison is made to the sequence of administering chemotherapy before DC vaccination.

Applicants submit that such a comparison is not required to establish surprising results. However, such a comparison is inherent in the data presented. As shown in Fig. 5, about one-third of the patients in the vaccine and the vaccine+chemotherapy group had received some form of chemotherapy prior to vaccination. If there were an additive or synergistic effect of administration of chemotherapy prior to vaccination, one might expect to have seen some advantage of the vaccine group as compared to the chemotherapy group. However, the time to initial recurrence for the vaccine group was not significantly different from that of patients in the chemotherapy group (Fig. 1B). Additionally, median survival was also not significantly different between the vaccine and chemotherapy groups (Fig. 2, Fig. 5). The only significant difference observed was when chemotherapy was administered following vaccination. Administration of chemotherapy following an initial recurrence clearly extended the time to

subsequent recurrence in the vaccine+chemotherapy group as compared to the vaccine only or chemotherapy only groups (Fig. 1B) and also increased overall survival (Fig. 2, Fig. 5).

Applicants submit that in view of the unpredictable nature of therapy for CNS cancers, the long-felt need for effective treatments, and the inventors' surprising results, the claims are patentable over the combination of Vitiello and Friedman.

Claims 5-7 were rejected as allegedly unpatentable over Vitiello in view of Friedman, and further in view of Liu et al., 2000, Clin. Cancer Res., 6:2585-97 ("Liu"). The Office (at page 6) presents Liu as disclosing "a method of treating glioblastoma multiforme in a patient comprising administering autologous DC primed ex vivo with tumor antigen at a dose of $10X10^6$ to $40X10^6$ three times (p. 308, col. 2)." However, as discussed above, claim 1 (from which claims 5-7 depend) is patentable over the combination of Vitiello and Friedman based on the unpredictable nature of CNS cancer therapy, the long-felt need for effective treatments, and the inventors' surprising results. Liu provides no teaching or suggestion to contradict these findings. In fact, Liu concurs that "there is a critical need to discover new therapeutic strategies that specifically target brain tumors" (p. 301, second column). Therefore, claims 5-7 are patentable over the combination of Vitiello, Friedman, and Liu.

CONCLUSION

Applicants submit that the claims are in condition for allowance and such action is requested. This response is being submitted with a Request for Continued Examination, a Petition for Extension of Time, and the required fees. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 22862-0004US1.

Respectfully submitted,

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